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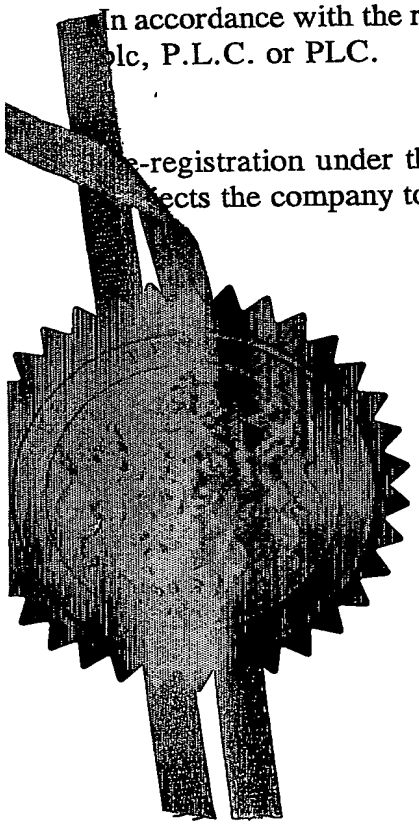

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Your reference	**500845GB01**
Patent application number *(The Patent Office will fill in this part)*	0422307.9
Full name, address and postcode of the or of each applicant *(underline all surnames)*	**BTG International Limited** **10 Fleet Place** **Limeburner Lane** **London** **EC4M 7SB** **GB**
Patents ADP number *(if you know it)*	7443872001
If the applicant is a corporate body, give the country/state of its incorporation	**GB**
Title of the invention	**GENERATION AND DELIVERY OF THERAPEUTIC MICROFOAM**
Name of your agent *(if you have one)*	**Paul Christopher SIMPSON**
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	**BTG International Limited** **10 Fleet Place** **Limeburner Lane** **London** **EC4M 7SB** **GB** 7443872001

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Paul Christopher SIMPSON

Name and daytime telephone number of person to contact in the United Kingdom **HATCHER, Aaron 020 7575 1728**

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Generation and delivery of therapeutic microfoam

The present invention relates to the generation of foam comprising a sclerosing material, particularly a sclerosing solution, which is suitable for use in the treatment of various medical conditions involving blood vessels, particularly varicose veins and other disorders involving venous malformation.

Sclerosis of varicose veins is based on the injection into the veins of liquid sclerosant substances which, by *inter alia* causing a localised inflammatory reaction, favour the elimination of these abnormal veins. Until recently, sclerotherapy was a technique selected in cases of small and medium calibre varicose veins, those with diameters equal to or greater than 7 mm being treated by surgery.

An injectable microfoam suitable for therapeutic use, on larger veins in particular, has now been developed and is described in EP-A-0656203 and US 5676962 (Cabrera & Cabrera), incorporated herein by reference.

As discussed in the Cabrera patents it is desirable from a safety standpoint for therapeutic foam for intravenous injection be made with gases which are readily dissolved and/or absorbed into the blood and specifically not air or any other gas mixture containing a significant proportion of nitrogen.

The co-pending applications mentioned above describe canister-based systems for generating therapeutic foam, where the liquid is stored under pressure under the gas which is to be incorporated into the foam. The canister systems produce excellent foam within a well-defined specification and the efficacy of foam from these devices has been demonstrated in extensive clinical trials.

WO 00/72821-A1 (BTG International Limited), incorporated herein by reference, describes the fundamental concepts underlying this canister product. The foam is produced by passing gas and sclerosant liquid through one or more meshes having small apertures measured in microns. Like the Cabrera patents, this document acknowledges the potential issues with air / nitrogen and seeks to reduce the levels of nitrogen in the foam. A microfoam is produced, having very small bubbles of a

defined size range and a defined density range. The microfoam may be produced by a single passage of the gas and liquid mixture through the mesh.

In a later patent application, WO 02/41872-A1 (BTG International Limited), incorporated herein by reference, the sclerosant liquid and an oxygen-rich physiologically acceptable blood dispersible gas are stored in separate containers until immediately prior to use, when the blood-dispersible gas is introduced into the container holding the sclerosant liquid.

The canister system has some drawbacks, however. It is relatively complex and thus expensive. Furthermore, the initial quantity of foam generated using a canister system can be of unpredictable quality and thus tends to be diverted off to waste prior dispensing foam for use. It is not easy to deliver foam direct from a pressurized canister into a cannula in a patient's vein; although this is theoretically possible, it would require special valve/control arrangements on the canister output to allow for the delivery rate to be highly controllable by the clinician administering the treatment. A further issue is that, whenever dispensing of foam is stopped or slowed significantly, it is necessary on re-starting to divert a quantity of foam to waste again before dispensing usable foam.

For all these reasons, the canister product mentioned above, though a well designed and highly effective system, is designed to deliver foam product into a syringe for subsequent administration to a patient. A special foam transfer unit is used for this purpose. The syringe nozzle is inserted into a port on this transfer device and the device is then used to divert the first portion of foam before charging the syringe with usable foam.

The above procedure takes time and requires a certain amount of training to carry out properly. A further issue is that the foam, once made, immediately starts to change - liquid drains out and bubbles coalesce. A period of time is required time for the clinician to divert an initial quantity of foam from a canister, charge a syringe with good foam, connect it to a line to a patient's vein and administer the foam. This time will vary with different clinicians and even the same clinician will not always take the same length of time. Furthermore, each treatment is different and the foam will be

injected over a different period; sometimes the clinician will stop dispensing foam for a short period and then recommence. All this time, the properties of the foam will be changing.

There are other techniques for generating foam for use in sclerotherapy, including the so called "Tessari" and "DSS" techniques, each of which involves pumping liquid sclerosant and gas between two syringes. These two techniques are widely used for generating sclerosing foams made with air, and there are also a number of other less widely used techniques. Although these techniques are simpler than a canister system, they offer no solutions to the problems mentioned above and they also have their own problems such as unpredictability of the product and the difficulty in using any gas other than ambient air.

The inventors realized that it would be desirable to have a device which could be connected directly to the patient and would generate foam as it was needed, so that the foam had the minimum possible time to degrade before entering a patient's vein. Ideally the device would also not have the problem of producing an initial quantity of poor foam. The device should be suitable for containing a gas other than air for incorporation into the foam.

The inventors also realized that, particularly for a highly soluble gas, the device should ideally not store the gas together with the liquid under a pressure substantially greater than atmospheric. With a soluble gas, especially a highly soluble gas such as carbon dioxide, storing the gas and liquid under pressure can contribute to the speed of decay of the foam. This is because the pressurised gas tends to go into solution in the sclerosant liquid. On exit of the foam, the gas comes out of solution into the bubbles thereby accelerating degradation of the foam. Pressurising the gas also, of course, adds to the complexity and expense of the system.

According to a first aspect of the invention, a device for generating and dispensing foam for therapeutic use comprises:

(a) a housing;

(b) the housing having a first chamber of adjustable volume containing gas at substantially atmospheric pressure;

(c) the housing further having a second chamber of adjustable volume containing sclerosant solution;

(d) an outlet for dispensing the liquid and sclerosant solution in the form of a foam and a flow path communicating between the outlet and the said first and second chambers;

(e) the flow path including a region in which mixing of the gas and solution takes place;

(f) a foaming unit located downstream of the mixing region, the foaming unit having holes with a dimension transverse to the flow direction of between 0.1 and 100 micron.

It is preferred that the hole dimension be from 1 to 50micron, more preferably 2 to 20micron, still more preferably 3 to 10micron. These holes may be provided by a mesh, perforated screen, sinter or fabric, for example. Although the shape and orientation of the holes may not be regular, the unit should have a major proportion (greater than 50%, preferably greater than 80%) of holes where at least one dimension in a direction approximately transverse to the flow should be in the ranges specified above.

Preferably the gas is at least 70% by volume carbon dioxide, more preferably at least 90% carbon dioxide, still more preferably substantially 100% carbon dioxide. The gas may also include oxygen. Alternatively the gas may be substantially 100% nitrous oxide or a mixture of nitrous oxide and carbon dioxide.

In use, the volumes of the first and second chamber are adjusted in order to drive the gas and solution out of the chambers and through the mixing region and foaming unit. A mixture of gas and solution is formed as the gas and liquid pass through the mixing region and then a foam is formed as the mixture passes through the foaming unit.

It is preferable for the liquid and gas to be driven through the mixing region and foaming unit at a flow rate which falls within a predetermined range, the desired flow rate range depending on the characteristics of the liquid and of the gas, the characteristics of the mixing region and foaming unit, and possibly other characteristics of the system. The volume of the chambers may be varied manually to

create the foam, but it is preferred that the adjustment of the chambers be carried out using some other source of motive power, e.g. an electric, clockwork, pneumatic or hydraulic motor or by the direct action of pressurized gas or even a simple spring. An on/off control is preferably provided for the user to commence and to stop delivery of foam.

The source of motive power may be provided as part of the device. Alternatively, the device may be designed as a cartridge for insertion into a delivery device which may for example be similar to known devices for automatically delivering medication from a syringe over an extended period of time.

The device may be configured with a flexible housing in form of e.g. a bag with dual chambers, or two separate bags, connected to a mixing region and foaming unit. The bag or bags may then be rolled up in a delivery device or the contents squeezed out by some other mechanical means. Desirably, the chambers are of a size and shape which allow them to be squeezed out at the same rate, in terms of velocity, to achieve a desired foam density. This allows the mechanical means for squeezing the chambers to be of a more simple design.

Alternatively the device may be configured as a syringe, with the first and second chambers having respective plungers which may be depressed in order to expel the contents. Preferably size and shape of the chambers, most notably their cross sectional areas, are selected so that the plungers may be driven at the same speed to achieve a desired ratio of gas to liquid in the foam.

As discussed above, the device may be suitable for connection to a cannula needle, optionally via a line, for delivery of foam into the body, e.g. into a vessel such as a blood vessel, especially a varicose vein or other venous malformation. Since the foam is generated by the same action which expels the foam from the outlet, it may be possible to connect the cannula to the outlet of the device and administer foam to a patient at the same time as generating it. This is clearly a much simpler procedure than generating the foam, drawing it up into a syringe, connecting the syringe to a line/cannula and then administering the foam.

According to the invention, a method for administering a foam to the human body, e.g. into a vessel such as a blood vessel, especially a varicose vein or other venous malformation, comprises the steps of:

(a) connecting a device as described above to a cannula needle inserted into a patient;

(b) adjusting the volume of the said first and second chambers so as to generate and deliver foam to the patient.

A further advantage of the generation and delivery of the foam in a single step is that the foam has very little time to degrade prior to entering the body to perform its function, e.g. the sclerosis of a varicose vein. The device is therefore particularly suitable for generating foams with very soluble gases, such as carbon dioxide or nitrous oxide, which tend to revert to their gaseous and liquid phases relatively quickly.

Since the gas and liquid are stored in separate chambers until formation of the foam, there is very little possibility for the gas to become dissolved in the liquid, which tends to happen with the pressurized canister systems described in the prior art.

According to the invention, a foam is provided which is made with a sclerosant solution, e.g. polidocanol solution, and a gas, wherein, on creation of the foam, the dissolved level of the gas in the solution is not substantially higher than that of the solution when exposed to atmosphere at s.t.p., and wherein the gas is at least 70% by volume carbon dioxide, more preferably at least 90% carbon dioxide, still more preferably substantially 100% carbon dioxide. The gas may also include 0.1 to 50% oxygen. Alternatively the gas may be substantially 100% nitrous oxide or a mixture of nitrous oxide and carbon dioxide.

[bubble spec & density]

Also according to the invention, a device is provided for generating foam from a sclerosant liquid, e.g. polidocanol solution, and a soluble gas as described above, wherein the device incorporates a chamber in which the gas is stored at substantially atmospheric pressure. Preferably, the device further comprises a chamber in which

sclerosant liquid is stored. Preferably, the device further includes a foaming unit for creating a foam from the gas and sclerosant liquid, the foaming unit having holes with a dimension transverse to the flow direction of between 0.1 and 30 micron [more than 30?]

Further features and advantages of the invention will be apparent from the following description of various specific embodiments, which is made with reference to the accompanying drawings in which:-

Figure 1 is a schematic representation of a syringe barrel part of a first embodiment of device in accordance with the first aspect of the invention, showing it in a sealed state for storage;

Figure 2 is a schematic representation of a cartridge for use with the syringe barrel of Figure 1;

Figure 3 is a schematic representation of a modified cartridge for use with the syringe barrel of Figure 1;

Figure 4 is a further schematic representation of the syringe barrel of Figure 1 with a cartridge of the type shown in Figure 3 being installed;

Figure 5 is a further schematic representation of the syringe barrel of Figure 1 with a foaming unit and plunger stem fitted;

Figure 6 is a schematic representation of the syringe, cartridge and foaming device of Figure 5, with the plunger stem of the syringe partially depressed;

Figure 7 is a schematic representation of a second embodiment of device in accordance with the first aspect of the invention, comprising charged syringe with foaming unit fitted;

Figure 8 is a schematic representation of the device of Figure 7 installed in a syringe driver for generation and delivery of foam at a controlled rate;

Figure 9 is a schematic representation of a third embodiment of device according to the invention;

Figure 10 is a schematic representation of the device of Figure 9 fitted to a motorized driver;

Figure 11 is a plan view of a mesh element of an embodiment of a foaming unit forming part of the invention;

Figure 12 is a side sectional view along the line I-I in Figure 11; and

Figure 13 is a side sectional view of an embodiment of foaming unit forming part of the invention.

A first embodiment of device according to the invention comprises a syringe type device comprising a syringe barrel having an annular chamber containing gas and a central chamber for receiving a cartridge of sclerosant solution, e.g. 1% polidocanol solution. Figure 1 shows a syringe barrel 1 in a storage condition with its open ends closed with seals 2 of metal/plastic laminate material. The barrel 1 comprises an outer cylindrical wall 3 having a conical tapered end portion 4 at the front, from which extends a standard luer nozzle 5. Disposed within the outer cylindrical wall is an inner cylindrical wall 6 defining an inner chamber 14. The front of the inner wall 6 is partly closed by and end face 8, in which is formed an orifice 9 with a frangible seal 10. The inner wall is supported at the front end by a web 11, in which apertures 12 are formed.

The outer and inner walls 3, 6 define between them an annular space 7 which is filled with substantially 100% pure carbon dioxide gas. The annular space 7 communicates with the interior space of the luer nozzle 5 via the apertures 12 in the web 11. Located at the rear of the barrel, in the annular space 7, is an annular plunger seal 13 of resilient plastics material which seals against the outer and inner cylindrical walls 3, 6.

Figure 2 shows a cartridge comprising a glass tube 20 filled with 1% polidocanol and sealed at each end by a resilient plastics bung 21. One or both of the bungs may function as a plunger seal, that is to say it may be movable down the length of the tube whilst retaining a sealing contain with the interior wall of the tube. The cartridge of Figure 2 is not suitable for use with the syringe barrel described above, but could be used with a modified version of the barrel as discussed below.

Figure 3 shows a cartridge suitable for use with the syringe barrel described above with reference to Figure 1. The cartridge comprises a glass tube 30 which is filled with 1% polidocanol solution. At the rear end of the tube 30 is a resilient bung 31 which is capable of functioning as a plunger seal as described above. At the front end of the tube is an end face 32 in which is located a nozzle 33, sealed with an end cap 34. The size and shape of the tube 30 complements the shape of the inner wall 6 of

the syringe barrel of Figure 1. In particular, the diameter of the tube 30 is such that the tube is a close fit in the interior space 14 defined within the inner wall 6 of the barrel 1, and the nozzle 33 of the cartridge is sized so that, when fully inserted into the interior chamber 14 of the barrel, it protrudes through the orifice 9 in the front of the chamber 14 (the end cap 34 having first been removed).

Cartridges of the type shown in Figures 2 and 3 are well known for liquid drugs. The cartridges are fitted to specially designed injection devices to administer the drug, and the empty cartridge then removed from the device and disposed of.

Figure 4 shows a cartridge 30 as shown in Figure 3 being inserted into the barrel of Figure 1. Note that the end cap 34 of the cartridge has been removed.

Figure 5 shows the cartridge 30 fully inserted into the barrel 1 such that the nozzle 32 seals in the orifice 9 of the interior chamber 14 of the barrel. A syringe plunger stem 40 is fitted to the rear of the syringe barrel 1. The plunger stem 40 comprises a disc 43 for applying manual pressure, connected via shafts 44 to a central disc shaped pressure pad 41 and an annular pressure pad 42. The pressure pads 41, 42 are engaged with bungs / plunger seals 31, 13, respectively, of the annular barrel chamber 7 and of the cartridge 30.

At the front of the barrel 1, a foaming unit 50 is fitted to the luer nozzle 5. The foaming unit comprises a stack of mesh elements with microscopic perforations. The foaming unit will be described in more detail below in relation to Figures 11, 12 and 13.

In use, the plunger stem 40 is depressed either manually or in a syringe driver such as the one shown schematically in Figure 8 and discussed below. The syringe with partly depressed plunger stem and foaming unit fitted is shown in Figure 6. The plunger seals 13, 31 in the annular carbon dioxide chamber and in the chamber defined within the cartridge are advanced as the plunger stem is depressed, thereby driving carbon dioxide and polidocanol solution through the apertures 12 and the orifice 9. Mixing of the gas and liquid takes place in the region 15 in front of the orifice 9 where the annular gas flow interacts with the liquid flow. The mixture then

proceeds as indicated by arrow A in Figure 6 through the syringe nozzle 5 into the foaming unit 50 where the gas and liquid are passed through microscopic perforations of average dimension 5micron to create a fine foam or microfoam with an average bubble size of around 100micron.

Figure 7 shows an alternative syringe-based design. A syringe barrel 101 houses twin parallel gas and liquid chambers 107, 114 which receive respective cartridges 170, 120 of the type shown in Figure 2 with resilient bungs 171a, 171b, 121a, 121b at each end. The gas chamber 107 contains cartridge 170 which is filled with substantially 100% pure carbon dioxide at substantially atmospheric pressure. The liquid chamber 114 contains cartridge 120 which is filled with 1% polidocanol solution.

At the rear end of the barrel 101 a plunger stem is fitted, comprising a disc 143 for applying manual pressure, connected via shafts 144 to two disc shaped pressure pads 41, 42 received within the gas and liquid chambers 107, 114 respectively.

At the front end of the syringe barrel is an end wall 104 from which projects a cylindrical hub 116 with a nozzle 105 at the end. Within the hub 116 is a mixing chamber or mixing region 115. In this region are located static mixing fins 117. Located at the front of the chambers 107, 114 are hollow needle-like members 118, 119 respectively, each with a point 118a, 119a facing into the respective chamber. Each needle-like member is contoured to lie along the front face of its respective chamber and to extend into the mixing chamber 115.

Fitted to the nozzle 105 of the syringe is a foaming unit 50 of similar design to that used in the device of Figures 1 to 6. The foaming unit will be described more fully below with reference to Figures 11-13.

The syringe is supplied with cartridges 120, 170 pre-fitted. A clip 119 prevents depression of the plunger stem 140 until the clip is removed immediately prior to use. When it is desired to use the syringe, the clip 119 is removed and the plunger manually depressed so that the cartridges 120, 170, which are a snug fit in their respective chambers 114, 107, are advanced into contact with the needle elements

119, 118 respectively. Further depression of the plunger stem 140 causes the needle points 119a, 118a to penetrate the resilient bungs 121a, 171a at the front of the cartridges, thereby opening a communication channel between the interior of the cartridges and the mixing chamber 115.

Further depression of the plunger stem 140 causes carbon dioxide and polidocanol solution to flow together into the mixing chamber, in a ratio predetermined by the cross-sectional areas of the cartridges. Fins 117 in the mixing chamber ensure that the gas and liquid are thoroughly mixed prior to entering the foaming unit 50 where the liquid and gas is converted into a microfoam.

When treating a patient, the clinician would go through the above steps and ensure that consistent microfoam is being discharged from the foaming unit 50. Pressure is then released from the plunger stem 140 and a line from a cannula, which has previously been inserted into a vein to be treated, is connected by a standard luer fitting to the exit of the foaming unit. Pressure would then be applied again to the plunger stem 140 to produce microfoam and at the same time inject it through the line and cannula and into the patient's vein.

The exact properties of the microfoam will depend to some extent on the speed at which the plunger stem 140 is depressed. For this reason it is preferable that a syringe driver is used to administer the foam. A syringe driver is shown schematically in Figure 8, with the syringe of Figure 7 fitted in it. The driver 200 comprises a base 201, syringe clamp 202 and motor 204 fitted in a motor mounting 203. The motor 204 is coupled via a coupling 209 to a drive shaft 206 having an external thread 210. Received on the drive shaft is annular member 207 having an internal thread 211 engaged with the external thread 210 of the drive shaft. From the annular member 207 extends a driving member which bears on the plunger stem 140 of the syringe which is clamped in the syringe clamp 202.

The motor is connected to a DC power supply 212, has a speed calibration control 209 for setting the correct drive speed, and also an on/off control 205.

In use, the clinician would remove the clip 119 from the syringe of Figure 7, depress the plunger stem 140 to the point where consistent microfoam is being produced, then insert the syringe into the driver and connect up to a line 80 previously installed in a patient's vein. The speed of the motor 204 would previously have been calibrated to a speed appropriate for the syringe being used. The clinician then has control of the delivery of microfoam to the patient by means of the on/off switch.

As short a line as possible is used, so that a very small quantity of microfoam resides in the line when the motor is switched off. In this way, it is ensured that almost all the foam delivered to the patient has been generated only a few moments previously and has had very little opportunity to degrade.

Figures 9 and 10 show an alternative embodiment 300 of foam generating and dispensing device. This embodiment is based on a bag 301 of metal / plastics laminate material. In the bag are located chambers 302, 303 separated by ultrasonically welded seams 310. The chambers 302, 303 contain carbon dioxide and 1% polidocanol solution respectively. The chambers are disposed in parallel along substantially the whole length of the bag, and the cross sections of the chambers, when filled, is selected so as to ensure a correct gas/air mix as with the syringe embodiments. Each chamber 302, 303 has a channel 304, 305 leading to a mixing region or mixing chamber 306 defined within a housing 307. On the front of the housing 307 is a luer nozzle 308, to which is fitted a foaming unit 50 as with previous embodiments. Within the mixing chamber 306 are located mixing fins 311.

At the rear of the bag 301 is a relatively stiff rod 309. In use, the bag 301 is rolled around the rod 309 to expel gas and liquid from the chambers 302, 303 respectively. As with previous embodiments, the gas and liquid enter the mixing chamber where they are well mixed before entering the foaming unit 50 and being converted to microfoam of preset density.

As with the other embodiments, the bag is preferably used with a driver device such as is shown schematically in Figure 10. In Figure 10 the bag 301 can be seen in side view, held in place on a movable carriage 321, slidably mounted on a base plate 320. The rear of the bag 301 is clamped by a bag clamp 322 at the rear of the carriage 321;

the rod 309 in this situation serves to help prevent the bag slipping through the clamp. The mixing chamber housing 307 at the front of the bag is clamped in a mixing chamber clamp 323 at the front of the carriage 321.

To set up the driver, the carriage, complete with bag, is slid sideways under a roller 324 mounted on the base plate 320. In order to do this, the bag is manually depressed at the rear end, adjacent the rod 309 to allow it to fit under the roller 324.

The roller 324 is driven by an electric motor 325 supplied from a DC power supply 326. The speed of the motor may be calibrated using speed control 327 and stopped and started using on/off switch 328.

On starting the motor, the roller rotates in the sense indicated by arrow B, causing the carriage, complete with bag, to slide under the roller. Gas and liquid contained in the bag is thereby forced through the mixing chamber 306 and foaming unit 50, and out of an exit of the foaming unit.

As with the previous embodiments, the clinician would ensure that consistent microfoam is being produced before connecting up a line 80 to a cannula installed in a patient's vein.

Referring now to Figures 11 to 13, the foaming unit comprises four mesh elements, each comprising a ring 51 having a mesh 52 secured across it. The mesh has perforations of diameter approximately 5micron. Each mesh element has male and female sealing surfaces 53, 54 respectively – these are best seen in Figure 12.

Figure 13 shows four mesh elements stacked together such that the male sealing surface of one element engages the female surface of the element next to it. The elements are retained in housing 55 having a socket half 56 and a nozzle half 57. Between these halves of the housing, the mesh elements are retained under pressure, with the sealing surfaces 53, 54 engaging with each other and with the interior of the housing 55 at each end. In this way a good seal is created between the mesh elements, so that all flow through the foaming unit must pass through the mesh.

The socket end 56 of the housing is formed with a standard luer socket 58 which, in use, fits over the luer nozzle output of the various devices described above. The nozzle end 57 of the housing incorporates a standard luer nozzle 59 onto which a medical line having a standard luer socket may be fitted.

Alternatives to the mesh elements described are contemplated: anything which provides pores, perforations, interstices, etc with a dimension in a direction approximately transverse to the direction of flow of between 0.1micron and 100micron may be suitable. Examples might include a fabric, perforated screen or sinter.

CLAIMS

1. A device for generating and dispensing foam for therapeutic use comprises:

(g) a housing;

(h) the housing having a first chamber of adjustable volume containing gas at substantially atmospheric pressure;

(i) the housing further having a second chamber of adjustable volume containing sclerosant solution;

(j) an outlet for dispensing the liquid and sclerosant solution in the form of a foam and a flow path communicating between the outlet and the said first and second chambers;

(k) the flow path including a region in which mixing of the gas and solution takes place;

(l) a foaming unit located downstream of the mixing region, the foaming unit having holes with a dimension transverse to the flow direction of between 0.1 and 100 micron.

2. A device as claimed in claim 1 wherein the gas is at least 70% by volume carbon dioxide, more preferably at least 90% carbon dioxide, still more preferably substantially 100% carbon dioxide.

3. A device as claimed in claim 1 or claim 2 wherein a source of motive power is provided to adjust the volume of one or both of the said chambers.

4. A device as claimed in any preceding claim taking the form of a syringe having twin plungers.

5. A device as claimed in claim 4 wherein the cross sectional area of the said first and second chambers are in a ratio of between 20:1 and 2:1.

6. A device as claimed in any of claims 1 to 3 taking the form of a flexible bag.

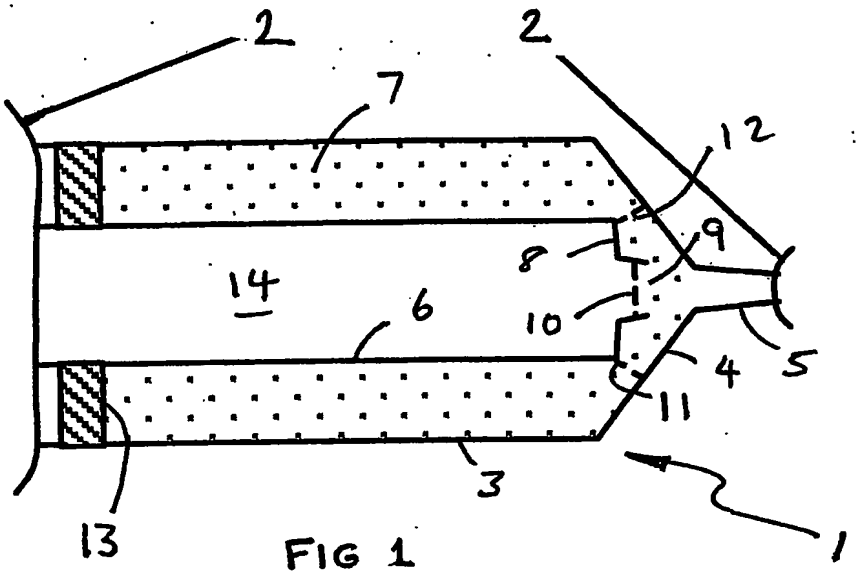


FIG 1

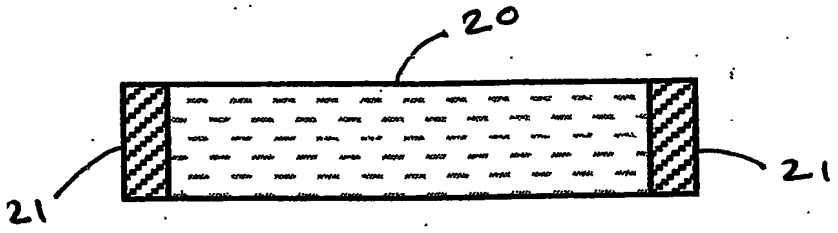
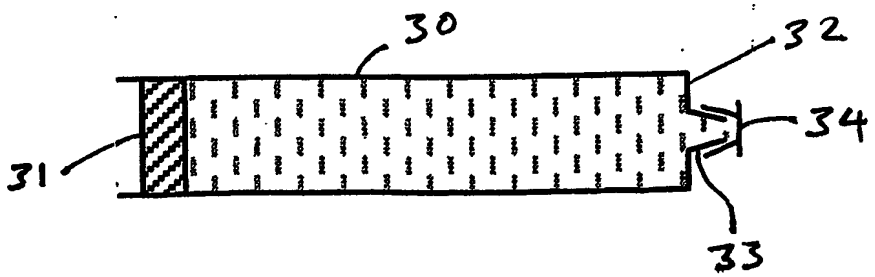


FIG 2



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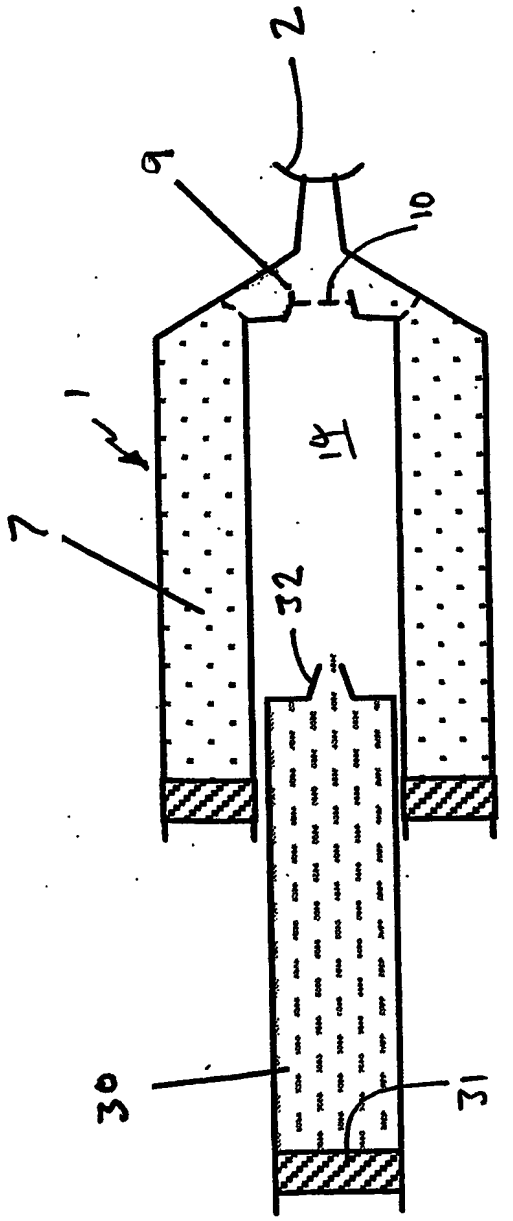

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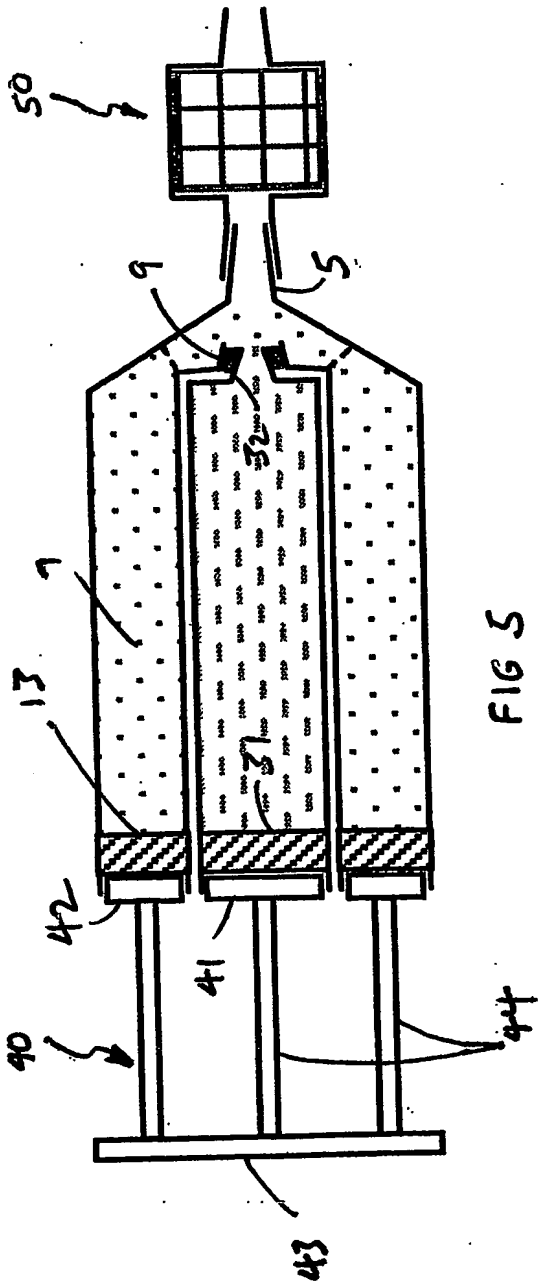
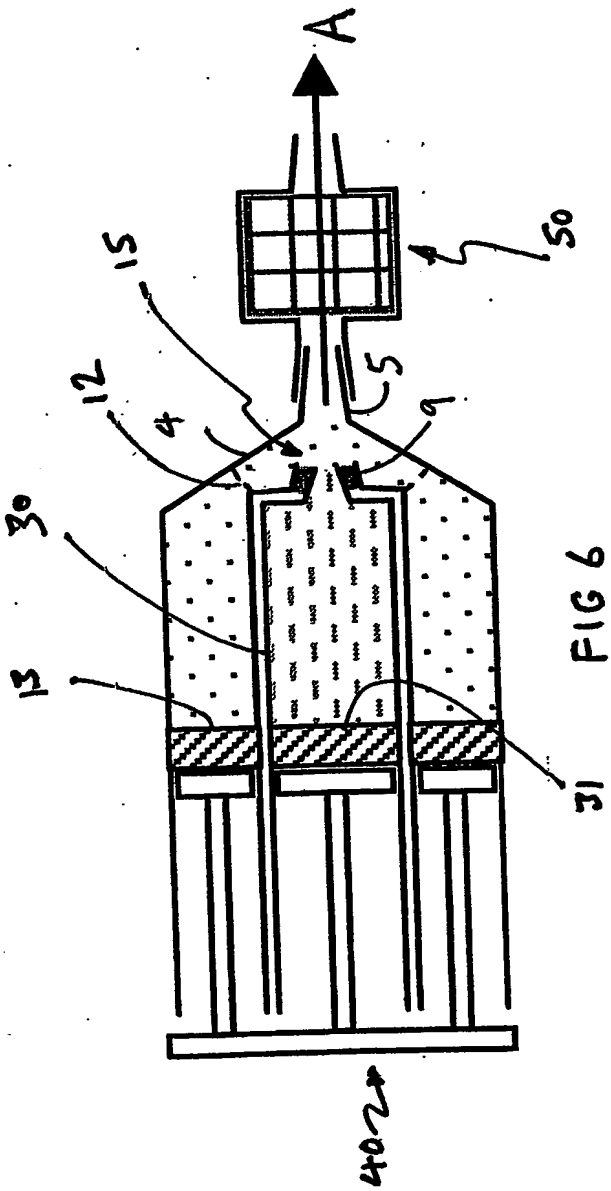


FIG 5



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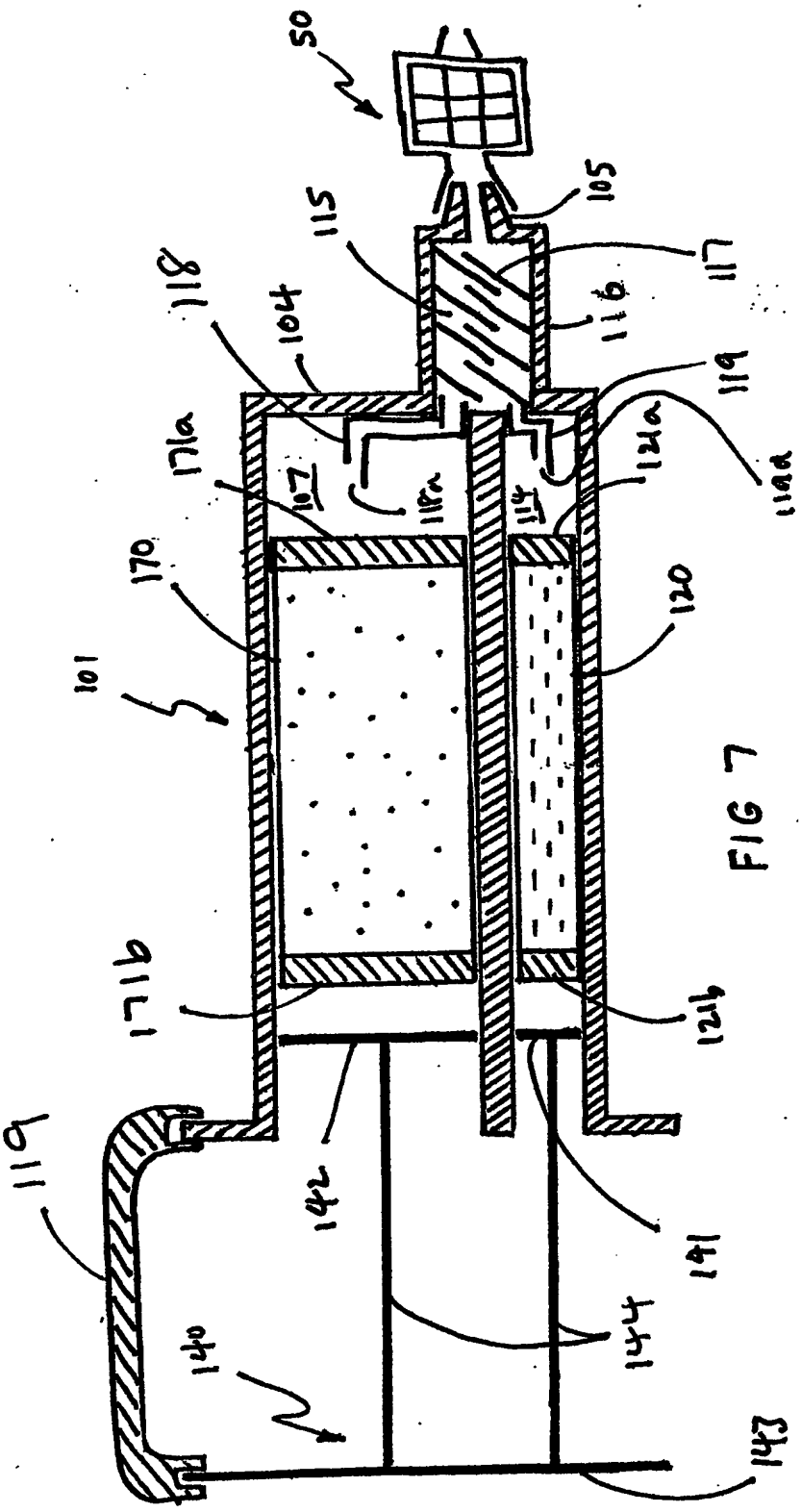
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FIG 7

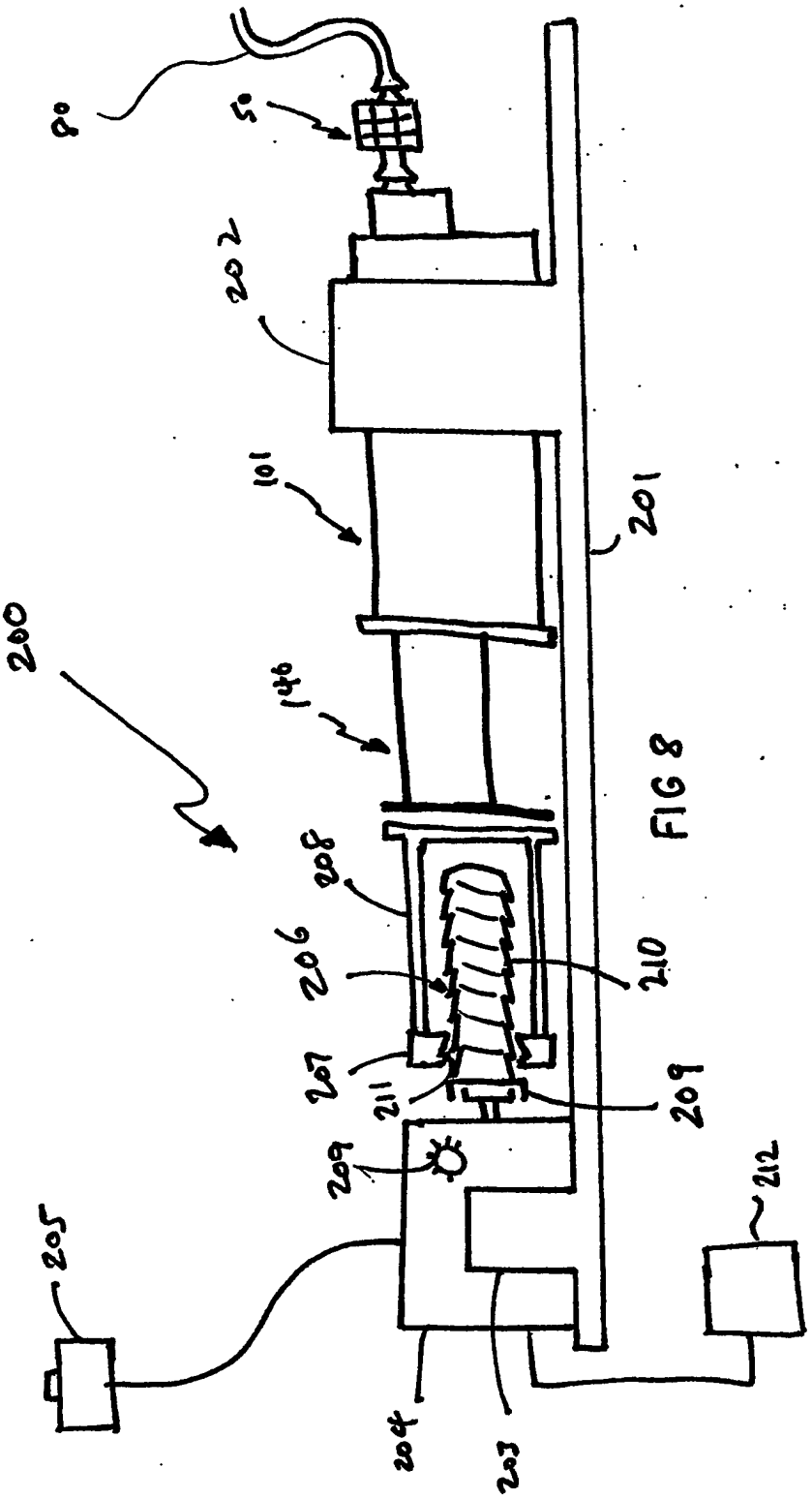
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FIG 8

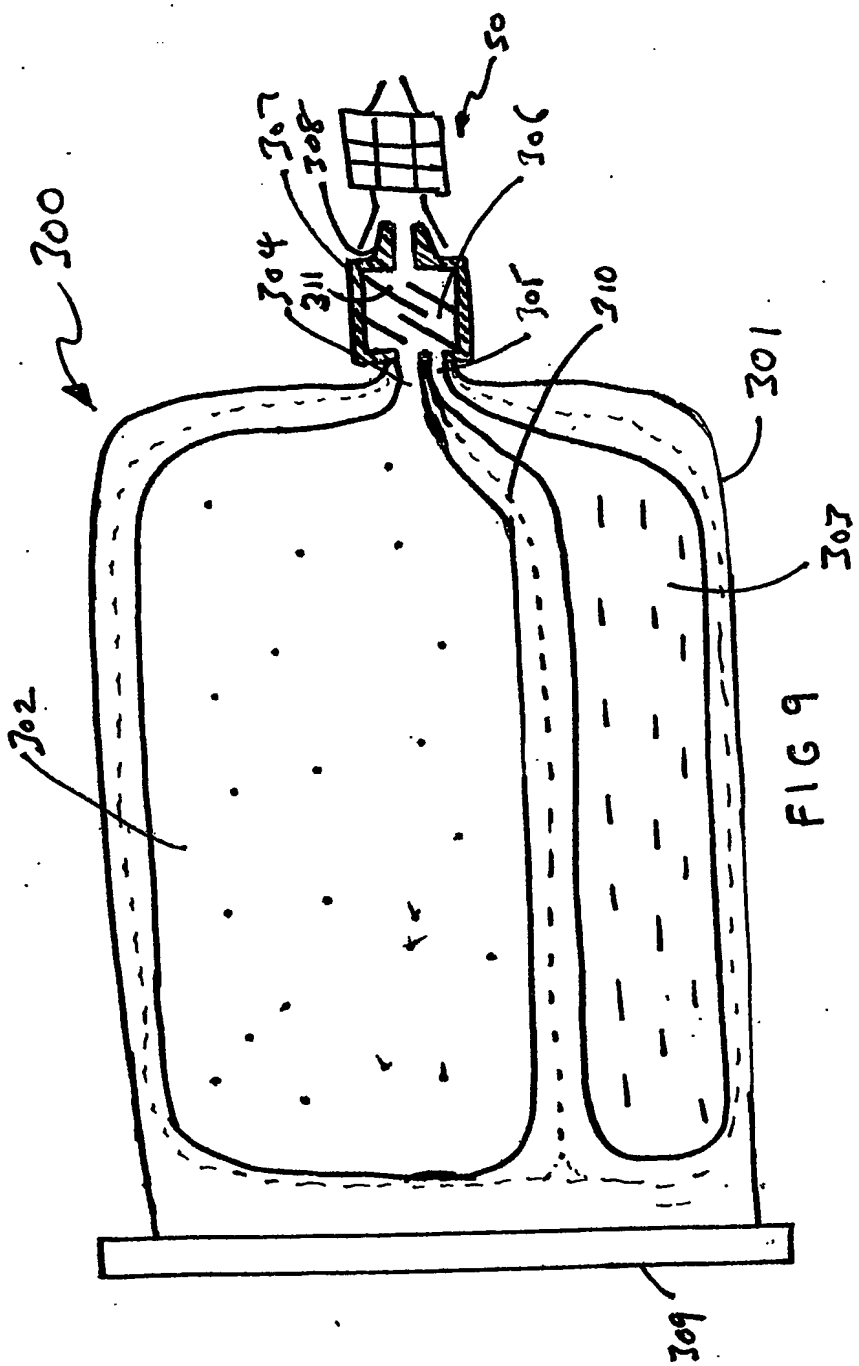
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FIG 9

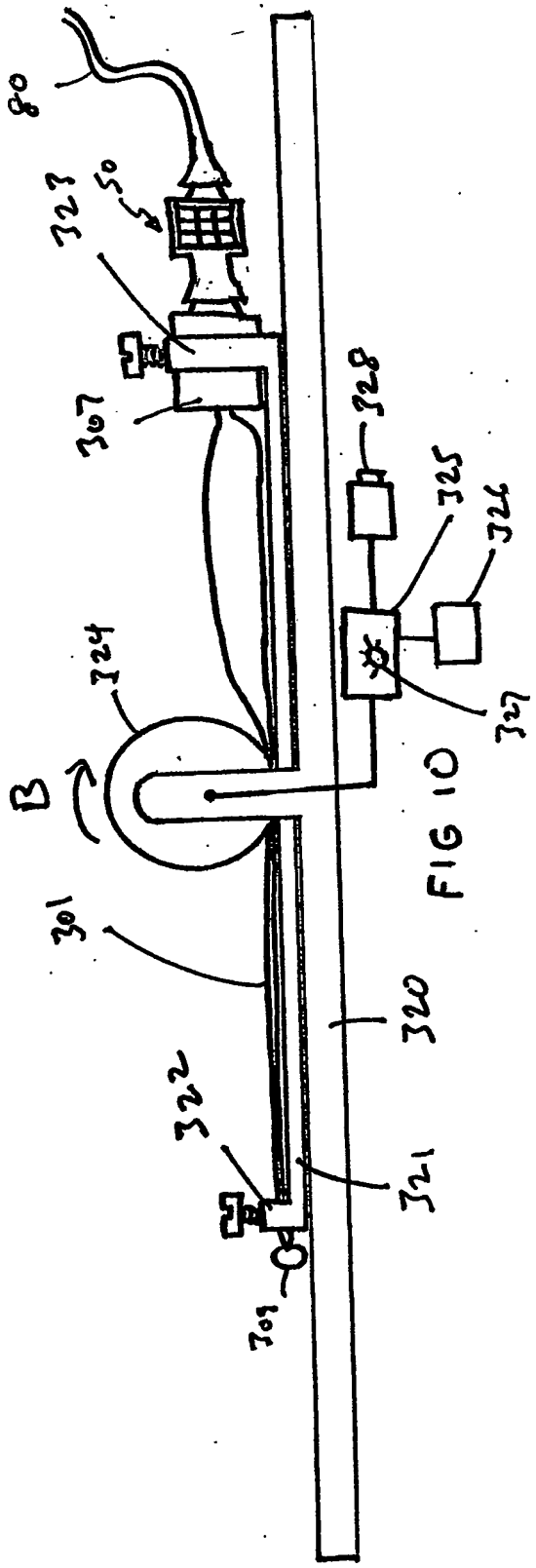
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FIG 10

Fig11

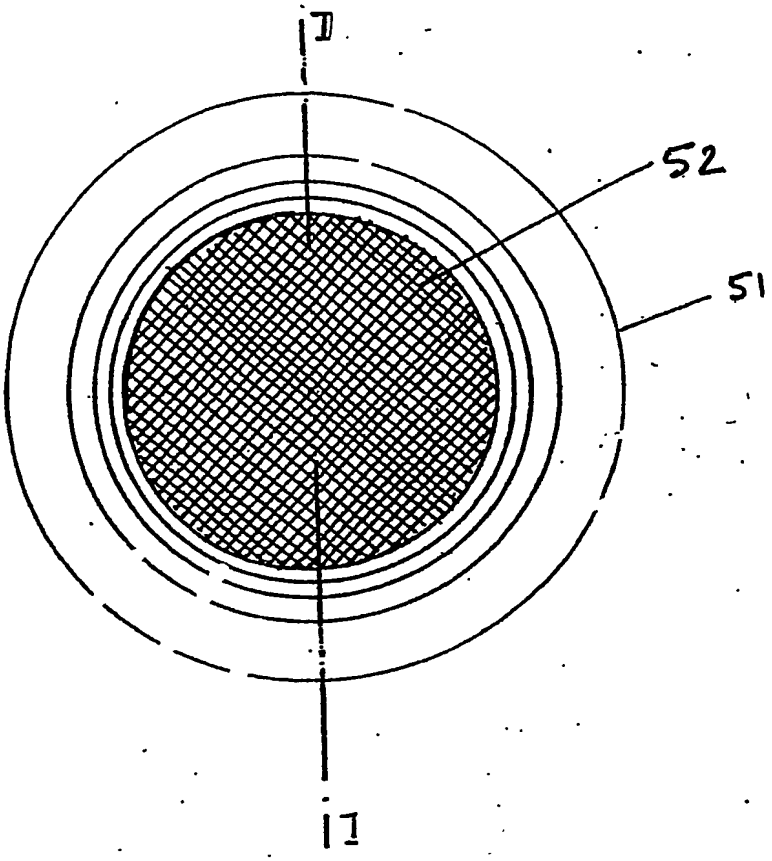


Fig12

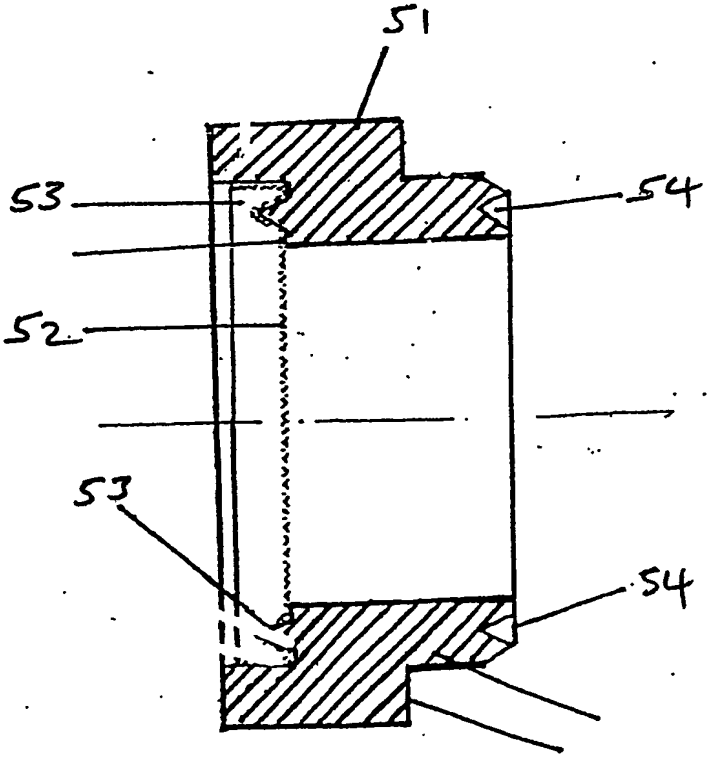
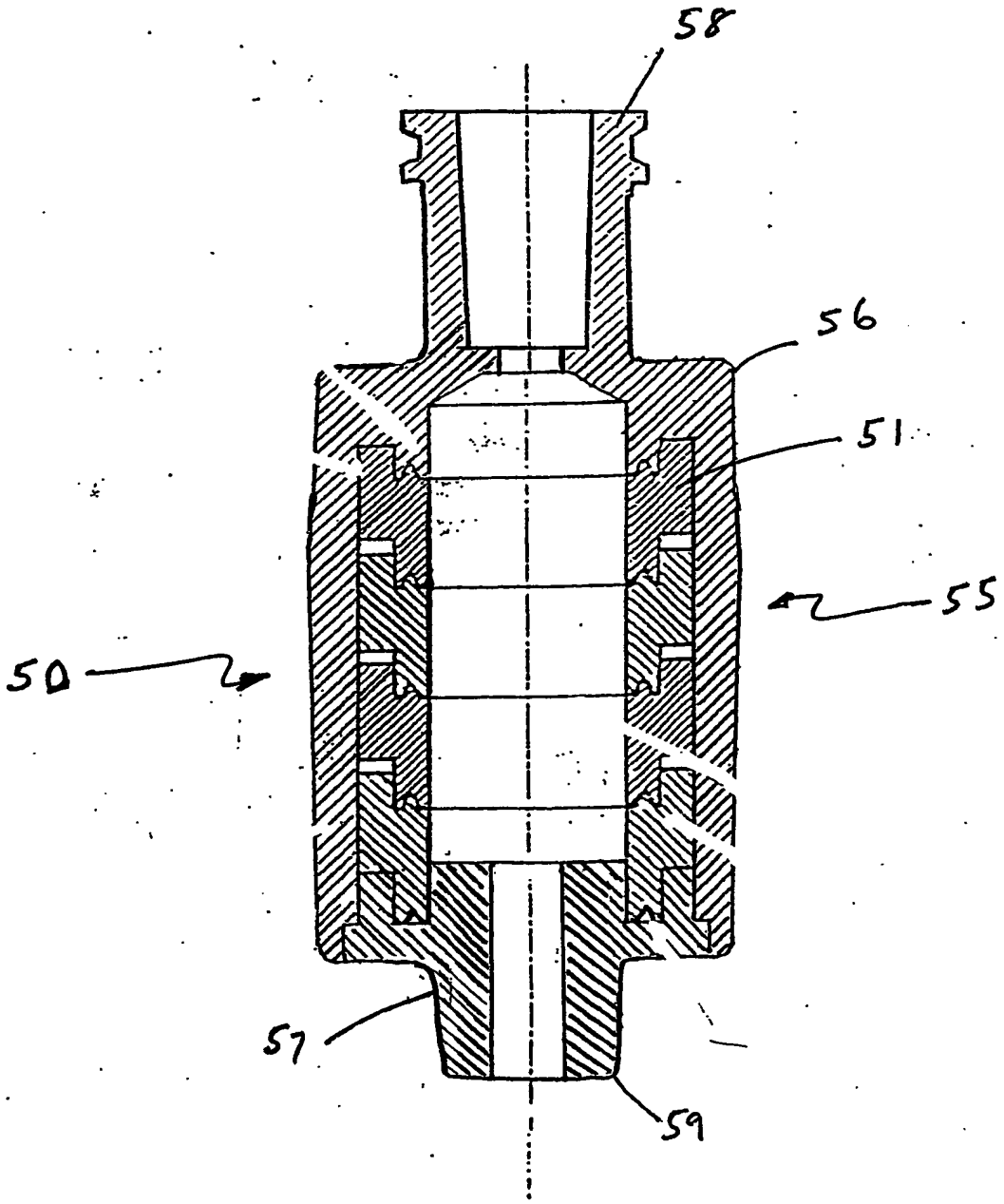


Fig. 13



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